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Review

Mitochondrial diseases and genetic defects of ATP synthase

Josef Houštěk *, Andrea Pícková, Alena Vojtíšková, Tomáš Mráček, Petr Pecina, Pavel Ješina

Institute of Physiology and Centre for Applied Genomics, Academy of Sciences of the Czech Republic, Vídeňská 1083, CZ 142 20 Prague, Czech Republic

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Abstract

ATP synthase is a key enzyme of mitochondrial energy conversion. In mammals, it produces most of cellular ATP. Alteration of ATP synthase biogenesis may cause two types of isolated defects: qualitative when the enzyme is structurally modified and does not function properly, and quantitative when it is present in insufficient amounts. In both cases the cellular energy provision is impaired, and diminished use of mitochondrial $\Delta\mu H^+$ promotes ROS production by the mitochondrial respiratory chain. The primary genetic defects have so far been localized in mtDNA *ATP6* gene and nuclear *ATP12* gene, however, involvement of other nuclear genes is highly probable.

Keywords: Mitochondrial diseases; ATP synthase; Biogenesis; ATP6; ATP12; Energy provision; Reactive oxygen species

1. Introduction

Inherited dysfunction of mitochondrial oxidative phosphorylation system is increasingly recognized as a frequent cause of human disease [1]. Most of the protein subunits of the mitochondrial respiratory chain are encoded by nuclear genes, while only 13, but essential, subunits are encoded by mitochondrial DNA (mtDNA). Mitochondrial energy provision thus uniquely depends on two genomes. Numerous nuclear and mtDNA mutations have been identified in affected patients to cause combined defects as well as isolated disorders of individual oxidative phosphorylation enzymes, including mitochondrial ATP synthase. Most isolated defects of ATP synthase are associated with alterations in the biosynthesis of the enzyme and can be caused by mutations in subunit genes or in ancillary proteins essential for the enzyme assembly. The ATP synthase is a key component of mitochondrial energy conversion in the mammalian organism as it produces most of the cellular ATP in aerobic cells. No wonder that pronounced defects of this enzyme result in mitochondrial diseases which are highly deleterious and manifest primarily in children, very often shortly after birth.

Abbreviations: ATP synthase, F_1F_o-ATP synthase; F_1 — catalytic part of ATP synthase, F_o — membrane sector part of ATP synthase; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; NARP, neuropathy, ataxia and retinitis pigmentosa

* Corresponding author. Tel.: +420 2 4106 2434; fax: +420 2 4106 2149.
E-mail address: houstek@biomed.cas.cz (J. Houštěk).

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2. ATP synthase biogenesis

Mitochondrial ATP synthase is composed of a catalytic F_1 part connected by two stalks with a membrane-embedded F_o part. The mammalian enzyme is built of at least 16 different subunits (F_1: $\alpha_3\beta_3\gamma\delta\varepsilon$+IF1, F_o: *a*, *b*, c_{10}, *d*, *e*, *f*, *g*, F_6, A6L, OSCP, (factor B)) [2–4] of which two F_o subunits — the subunit *a* (subunit 6) and subunit A6L are encoded by mitochondrial DNA (mtDNA). ATP synthase complex is formed stepwise with the assistance of several assembly factors but the mechanism of how the mammalian ATP synthase assembles from individual subunits is still not well understood. In the case of F_1, a close similarity of its structure in all types of energy-transducing membranes suggests an analogous assembly mechanism in mammalian cells, lower eukaryotes and prokaryotes. Concerning the F_o, the situation is complicated by increasing evolutionary complexity of the F_o structure, which gained 7 new subunits from bacteria to man. Most of the present knowledge of mitochondrial ATP synthase biogenesis originates from studies in yeast but the assembly process in mammalian cell might be modified as there are substantial differences between higher and lower eukaryotes such as the number and location of F_o subunit *c* genes, ATP synthase-specific assembly factors, or factors regulating transcription of mtDNA-encoded ATP synthase genes.

It has been shown that F_1 assembles in mitochondria of a yeast cytoplasmic *petite* mutant producing nonfunctional F_o [5]

as well as in mammalian rho^0 cells [6], but functional proton channel of the F_o portion has not been observed in mitochondria lacking the β subunit [7]. Ordered assembly of the yeast F_o sector was demonstrated using mutants for the mitochondrially encoded subunits [8]. A principal role of subunit 9 (subunit *c*) was suggested as in its absence subunits 6 and 8 (equivalent to A6L) were not associated with the enzyme complex. Sequential addition of mitochondrially-synthesized subunits was proposed to start with subunit *c*, followed by subunit 8 and then subunit 6. Moreover, subunit 6 was absent in cells devoid of any of the stator-stalk subunits: subunit *b* [9], OSCP [10] and subunit *d* [11], which might assemble in the order of *b*, OSCP and subunit *d* [12].

Similarly, in human cells, the incorporation of subunit 6 appears to be at the late stage of enzyme assembly (Fig. 1), as shown by the composition of assembly intermediates in cells with doxycycline-arrested mitochondrial protein synthesis [13], 8993 mutation in *ATP6* gene [14,15] or diminished content of subunit 6 due to altered processing of the *ATP6-COX3* transcript [16]. Combination of pulse-chase labelling and two-dimensional electrophoretic methods led to the following scheme: assembly starts with the formation of F_1, which then directs a sequential assembly of the membranous part. After the attachment of F_1 to subunit *c*, subcomplexes are formed, involving other nuclear-encoded subunits including subunits *b*, OSCP and F6. The incorporation of mitochondrially encoded subunits 6 and A6L completes the formation of the ATP synthase [13].

ATP synthase assembly depends on the assistance of multiple proteins that have substrate-specific chaperone-type functions. Altogether 5 factors have been identified in yeast, of which Atp11p and Atp12p mediate the formation of the F_1 moiety via interaction with subunits β and α, respectively (for review see [17]). The role of Fmc1p in F_1 assembly is less clear [18]. Atp10p and Atp22p are essential for the formation of the F_o part during which Atp10p assists in the incorporation of the subunit 6 [19,20]. In mammalian cells only the orthologues of yeast *ATP11* and *ATP12* but no F_o-specific assembly factors have been found [21,22] (Fig. 1). Nevertheless, the existence of specific factors involved in mammalian F_o formation is quite probable.

Further steps in the mammalian ATP synthase biogenesis include generation of dimers with the aid of subunits *e* and *g* [23], formation of higher oligomers (V1–V4) [24] and possibly also supercomplexes with other inner mitochondrial membrane proteins, e. g. with phosphate and adenine nucleotide carriers in the "phosphorylating assembly" — so called ATP synthasome [25,26]. Moreover, numerous recent studies identified ectopic location of ATP synthase on the plasma membrane surface of several types of mammalian cells. While the experimental evidence for the functional involvement in intracellular signalling as a receptor for apolipoprotein A-I [27], angiostatin [28], or enterostatin and beta-casomorphin1-7 [29] of ectopic ATP synthase in different cell types is quite convincing, nothing is known about the mechanism by which the ATP synthase gets there. It might possibly be transferred from mitochondria as a complete enzyme by membrane fusion.

The cellular content of mammalian ATP synthase relative to other respiratory chain enzymes is rather stable in many tissues, and biogenesis of ATP synthase requires coordination of nuclear and mitochondrial genomes and generally shares the common regulatory cascades with other mitochondrial oxidative phosphorylation complexes [30,31]. Up- and down-regulation of ATP synthase biogenesis involves both transcriptional and posttranscriptional regulation [32]. The amount of ATP synthase may be controlled by the availability of subunit *c*. This was demonstrated in the thermogenic brown fat where the ATP synthase content was physiologically reduced up to 10-fold due to depressed transcription of subunit *c* gene [33]. It has been further shown that *c* subunit overexpression can restore, at least in part, the ATP synthase content in brown fat. The expression of subunit *c* genes seems to determine the ATP synthase content in other tissues as well [34,35]. Indeed, the existence of differently organized [36] and regulated [34] isogenes coding for identical subunit *c* would be advantageous for multiple factor regulation of *c* subunit synthesis and thus ATP synthase biogenesis.

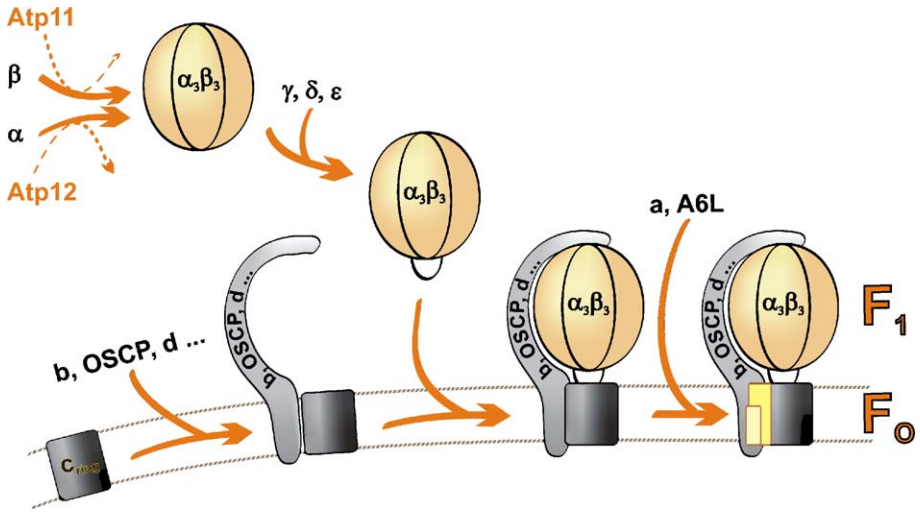

Fig. 1. Assembly of the mammalian ATP synthase. ATP synthase is formed in several successive steps. Assembly of the F_1-part is dependent upon the assistance of specific ancillary factors, Atp11 and Atp12, not belonging to the final complex. In the yeast enzyme, additional factors have been described to be involved in the formation of F_1 (Fmc1p) and F_o (Atp10p, Atp22p).

3. Qualitative and quantitative defects of ATP synthase

Generalized decrease in the content of human ATP synthase or alteration of its structure and function are associated with severe pathological states resulting in typical mitochondrial diseases. There are two types of isolated deficiency of ATP synthase that have been described, differing in the pathogenic mechanism, biochemical phenotype (structural and functional) as well as in clinical presentation.

The first, and long well-known type, are qualitative defects of ATP synthase caused by mutations in one of mtDNA-encoded ATP synthase subunits — the protonophoric subunit 6 [37]. Maternally transmitted mutations in the *ATP6* gene are heteroplasmic and pathogenic phenotype correlates with their mutation load [38]. Of the five missense mutations described so far, the T8993G mutation that leads to the $Leu^{156} \rightarrow Arg$ exchange is the most harmful (see [39]). At a high mutation load, up to approximately 95%, it manifests as neuropathy, ataxia, and retinitis pigmentosa (NARP) or as fatal encephalopathy known as Leigh syndrome [40]. Subunit 6 operates together with the ring of subunits *c* as the F_o proton channel and proton translocation from the intermembrane space to the matrix induces *c* ring rotation that is transmitted to the F_1 moiety, thus driving ATP synthesis [41]. *ATP6* missense mutations prevent ATP synthesis but the reverse reaction, ATP hydrolysis, is possible. On the basis of subunit *a* mutation in bacteria it has been proposed that the H^+ translocation is impaired [42] but later on it was shown that NARP cells are capable of ATP-driven H^+-translocation [43] and that mutated F_o can translocate protons from the cytosol to the matrix side of the inner mitochondrial membrane [44]. Therefore, it appears that *ATP6* mutations disturb the intraenzyme coupling of H^+-transport with the *c*-ring rotation and ATP synthase is unable to utilize the proton translocation down the membrane proton gradient for the phosphorylation of ADP.

A different form of qualitative ATP synthase deficiency is represented by another type of *ATP6* mutation, microdeletion of TA in position 9205–6 (ΔTA9205). This mutation is very rare, only two cases having been found to date [16,45]. In mammalian mtDNA the 5′-part of the *ATP6* gene partly overlaps with the *ATP8* (A6L) gene and the 3′-end is followed by the *COX3* gene. A primary tricistronic transcript is cleaved and polyadenylated to mature *ATP8/ATP6* bicistronic mRNA and *COX3* mRNA. The hypothesis that the mutation removes the STOP codon of *ATP6* and also the cleavage site between *ATP6* and *COX3* transcripts [45] was confirmed in a patient with severe encephalopathy [16] where a several-fold decrease of *ATP6* and *COX3* mRNAs was found. It resulted in diminished synthesis and cellular content of subunit 6, thus producing subunit 6-less enzyme capable of hydrolyzing but not synthesizing ATP. Absence of subunit 6 also interfered with the assembly mechanism leading to the accumulation of incomplete assemblies [16], similar to those observed in cells with T8993G mutation or cells with doxycycline-inhibited translation of mtDNA-encoded proteins. The primary problem in ΔTA9205 mutation seems to be the tricistronic *ATP8/ATP6-COX3* transcript processing. Interestingly, this was only little affected in the other homoplasmic case [46], which also differed biochemically and clinically in normal biosynthesis of subunit 6, unaltered mitochondrial ATP production [47] and very mild presentation of transient hyperlactacidemia. This unexplained difference in the manifestation of *ATP6* homoplasmic mutation indicates the existence of a factor, as yet unknown, that is apparently involved in mitochondrial *ATP6-COX3* mRNA processing.

The second currently known type of isolated disorders of ATP synthase are quantitative defects in which the cellular content of the enzyme is selectively reduced to less than 30% of the control, relative to the content of respiratory chain enzymes [48]. The disorder is of nuclear genetic origin, patients do not show any mutations in mtDNA *ATP6* and *ATP8* genes, and ATP synthase content is fully restored by replacement of the nucleus in transmitochondrial cybrids [49]. The biosynthesis of ATP synthase is inhibited but the expression of genes coding for enzyme subunits is not changed, including the level of transcripts of subunit c. Unlike *ATP6* mutations, the ATP synthase-deficient cells do not show accumulation of any incomplete assemblies, and it has been

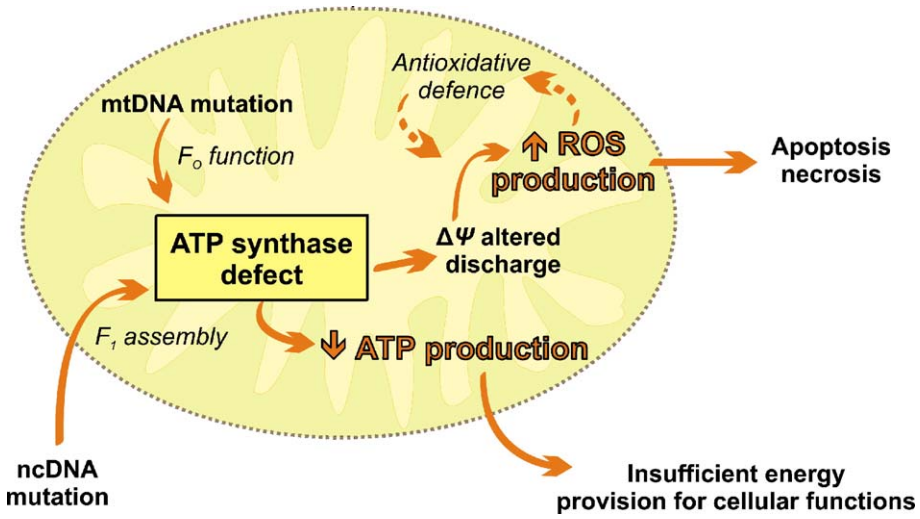

Fig. 2. Pathogenic mechanism of ATP synthase defects — energy deprivation and increased ROS production.

concluded that the problem lies in an early stage of enzyme assembly when the F_1 is formed [49]. At present, more than dozen patients with ATP synthase deficiency have been diagnosed [48–53]. Most of them display a remarkably uniform phenotype with an early onset already in newborns, severe and often fatal hyperlactacidemia, hypertrophic cardiomyopathy and elevated levels of 3-methylglutaconic acid in urine. About half of the patients die within the first days or months of life; however, long survival even for years, is also possible. Degenerative necrotic changes in the brain stem, typical of *ATP6* mutations, are rare. Detailed investigation of F_1 assembly factors showed in one case with pronounced brain atrophy a homozygous TGG-AGG missense mutation in exon 3 of *ATP12* changing Trp^{94} to Arg in the Atp12p assembly factor [53]. However, in others, clinically distinct case mutations in *ATP11* and *ATP12* were excluded, and normal expression of the F_1-assembly genes was found. Interestingly, this contrasts with the situation of ATP synthase-poor brown adipose tissue where *ATP12* mRNA is highly upregulated [54]. Apparently, the quantitative disorders of ATP synthase are caused by different genetic defects that remain to be identified. They may include additional mammalian ATP synthase-specific assembly factors that have not yet been recognized.

4. Two components of the pathogenic mechanism in ATP synthase disorders

Both types of ATP synthase disorders result in a decreased ability of mitochondria to produce ATP in patient cells. This has been clearly shown for *ATP6* mutations as well as for quantitative defects of ATP synthase. In milder mutations of *ATP6*, the ATP synthesis is clearly less affected than in the T8993G patients [14,15,55–58]. Experiments with T8993G cybrids and fibroblasts revealed an up to 5- to 20-fold decrease in ATP production at or near to homoplasmic state. A similarly pronounced decrease has been found in quantitative defects of ATP synthase that display only 10–30% of normal enzyme content. Substrate-supported mitochondrial ATP production in permeabilized cells was decreased to 30% or even more, depending on the substrates [49,51]. Indeed, in both types of ATP synthase disorders the ATP production measurements have been performed in cells that are largely glycolytic, such as cultured fibroblasts, cybrids or blood cells. The key question is how the altered function of ATP synthase affects the ATP production in patient tissues in vivo and how important it is for biochemical and clinical phenotype of the disease. The mainly affected tissues, brain and heart, primarily rely on oxidative metabolism and it is expected that a decline of aerobic energy provision can have deleterious effects on their function and morphology. Studies in mice indicate that due to nonlinear dependence of coupled respiration on ATP synthase content, significant ATP synthesis is to be expected even when the ATP synthase activity is very low. This is apparent from ATP synthase threshold values in different tissues [59,60]. Similar data for human tissues are missing, but even here, there must exist a significant spare capacity of ATP synthase, otherwise the patients with ATP synthase content reduced to 10% of the control would not be able to survive at all.

The low ability of mitochondria to utilize respiration-generated proton gradient for ATP synthesis generally means that the mitochondrial membrane remains hyperpolarized, which may lead to increased generation of reactive oxygen species (ROS) by the respiratory chain [61]. It has been demonstrated that the cells with *ATP6* mutations maintain high values of $\Delta\Psi$ [51,57] and also the cells from patients with quantitative defects of ATP synthase displayed increased $\Delta\Psi$ in state 3 (ADP) as well as in state 4 [49,62]. In both types of ATP synthase disorders, it was also documented that high $\Delta\Psi$ values indeed cause increased ROS production. The T8993G mutation caused an increase in MnSOD and in ROS levels determined with the fluorescent probe DCFDA [57,63]. Similarly, cells with quantitative defects of ATP synthase showed elevated levels of ROS and upregulation of antioxidative defence components [48,62]. Importantly, increased ROS production in both types of disorders was prevented by the uncoupler FCCP, indicating that it was the high membrane potential that upregulated the ROS production.

For a long time, uncompensated ROS production has been implicated in the pathogenesis of human mitochondrial diseases [64]. Now it appears that, besides complex I defects [65–67], the increased oxidative stress represents an important factor of the molecular pathogenic mechanism also in isolated disorders of ATP synthase. Thus, energy deprivation and elevated ROS production are the two major components of the pathogenic mechanism in isolated defects of ATP synthase that are closely related to each other (Fig. 2). At present, it is difficult to say which one is more important for the manifestation of the disease and whether a different proportion between ROS production and decline in mitochondrial ATP synthesis can be responsible for distinct clinical phenotypes in qualitative and quantitative ATP synthase disorders. Nevertheless, different types of antioxidants, such as perfluoro-tris-phenylnitrone, N-acetylcysteine, dihydrolipoic acid or Coenzyme Q_{10}, had an apparent beneficial effect on the level of ROS production, the cell viability, occurrence of apoptotic markers and even ATP production in NARP cells with T8893G mutation [57,63], which makes the ROS production a promising target for the therapy in isolated disorders of ATP synthase.

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